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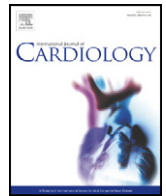
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# Heart failure and inflammation-related biomarkers as predictors of new-onset diabetes in the general population



Navin Suthahar<sup>a</sup>, Wouter C. Meijers<sup>a</sup>, Frank P. Brouwers<sup>a</sup>, Hidde J.L. Heerspink<sup>c</sup>, Ron T. Gansevoort<sup>b</sup>, Pim van der Harst<sup>a</sup>, Stephan J.L. Bakker<sup>b</sup>, Rudolf A. de Boer<sup>a,\*</sup>

<sup>a</sup> Department of Cardiology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands

<sup>b</sup> Department of Nephrology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands

<sup>c</sup> Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands

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## ABSTRACT

**Background:** There is a strong reciprocal relationship between heart failure (HF) and diabetes mellitus (DM). Shared pathophysiological mechanisms might be a possible explanation. Therefore, we hypothesised that biomarkers linked to HF would also predict new-onset type 2 DM in the general population.

**Methods and results:** We utilized the Prevention of Vascular and Renal End-stage Disease (PREVEND) cohort (mean age 48.9 years, 51% female) to study the relationship between HF and DM in 7953 participants free of baseline HF and DM. Multiple HF-related, inflammation-related and renal function-related biomarkers were evaluated regarding their predictive utility in new-onset DM. Incidence of DM in participants who developed HF was 11.8%, versus 5.4% in those who had not developed HF ( $p < 0.001$ ). Incidence of HF in participants who developed DM was 8.5%, versus 3.8% in those who had not developed DM ( $p < 0.001$ ). Classical HF biomarkers, NT-proBNP and hs-TnT were not associated with an increased risk for new-onset DM. However, inflammatory biomarkers hs-CRP [hazard ratio (HR) 1.16, (95% CI 1.05 to 1.29),  $p = 0.005$ ], procalcitonin [HR 1.34, (95% CI 1.07 to 1.69),  $p = 0.012$ ] and PAI-1 [HR 1.55, (95% CI 1.37 to 1.75),  $p < 0.001$ ] remained significantly associated with new-onset DM, even after multivariable adjustment for established predictors of DM.

**Conclusions:** Although HF and DM have a strong correlation with each other, systemic biomarkers that predict HF do not have a predictive value in new-onset DM. This suggests that other, indirect, pathophysiological mechanisms related to inflammation may explain their strong relation.

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## 1. Introduction

Heart failure (HF) is a complex clinical syndrome characterized by impaired circulation and systemic neurohormonal activation. Despite improvements in therapy and management its global prevalence is rising, rendering HF a serious health problem with a 5-year mortality of around 50% and a 10-year mortality of around 75% [1,2].

HF and diabetes mellitus (DM) have several common risk factors and shared pathophysiological mechanisms, and recent literature mounts significant evidence on the reciprocal relationship between HF and DM. The incidence of HF in patients with DM is higher than in the general population; there is approximately a 2.5 fold increased risk of contracting HF in diabetics than in healthy individuals [3]. HF is also an insulin resistant state [4,5] and patients with HF develop type 2 DM (T2DM) more often [6]. Insulin resistance associated with HF can be localized to the myocardium (myocardial insulin resistance) or it

could be generalized, affecting multiple organ systems [7]. Insulin resistance developing in HF might, however, be a reversible state: HF patients on ventricular assist device (VAD) demonstrated a significant improvement in their glycaemic parameters [8]. Therefore, our study aimed to examine whether classic HF biomarkers have a predictive value in new-onset DM, or if other domains (e.g. neuroendocrine activation, endothelial activation, fibro-inflammatory axis and renal axis) might better reflect the complex pathophysiology of HF and DM.

## 2. Methods

The PREVEND (Prevention of Renal and Vascular ENd-stage Disease) study is a prospective Dutch cohort taken from the general population of Groningen, the Netherlands between the year 1997 and 1998. An in-depth description of the PREVEND study can be found elsewhere [9–11].

From the baseline cohort ( $N = 8592$ ), patients with baseline DM ( $N = 331$ ) and participants with no follow-up data or who could not be linked to a pharmacy registry ( $N = 289$ ) were excluded. Patients with baseline HF ( $N = 19$ ) were also excluded, generating a final total of 7953 individuals free of DM and HF with complete follow-up data for DM. The PREVEND study is in accordance with the principles charted out in the Helsinki declaration. Approval from the local medical ethical committee was obtained and informed consent was provided by all participants, including the consent to link their data with pharmacy-dispensing data.

\* Corresponding author at: Department of Cardiology, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands.  
E-mail address: [r.a.de.boer@umcg.nl](mailto:r.a.de.boer@umcg.nl) (R.A. de Boer).

### 2.1. Procedures

Participants attended two outpatient sessions between 1997 and 1998 which constituted the baseline examination. Study subjects fasted before the visit (water or tea was allowed) and provided a first morning urine sample. Venous blood was drawn into EDTA tubes; aliquots were made and stored at  $-80^{\circ}\text{C}$  until analysis. The biomarkers tested were high-sensitive troponin-T (hs-TnT) [12], N-terminal pro-B-type natriuretic peptide (NT-proBNP) [13], mid-regional pro-A-type natriuretic peptide (MR-proANP) [14], C-terminal pro-endothelin-1 (CT-proET-1) [15], renin [9], aldosterone [9], C-terminal pro-arginine vasopressin (copeptin) [16], mid-regional pro-adrenomedullin (MR-proADM) [17], high-sensitive C-reactive protein (hs-CRP) [18], procalcitonin [19], plasminogen activator inhibitor-1 (PAI-1) [20], galectin-3 [21], urinary albumin excretion (UAE) [22], serum creatinine [17] and cystatin-C [17]. Details of the assays can be found in the data supplement. The first follow up session was done in  $4.2 \pm 0.4$  years, the second follow-up in  $6.5 \pm 0.7$  years and the final follow-up in  $9.5 \pm 0.8$  years after the baseline examination. The total follow-up period was  $11.4 \pm 3.2$  years.

### 2.2. Definitions

Incident T2DM was defined as a fasting plasma glucose  $\geq 7.0$  mmol/L (126 mg/dL), random sample plasma glucose  $\geq 11.1$  mmol/L (200 mg/dL), self-reporting of a physician diagnosis or initiation of glucose-lowering medication use retrieved from central pharmacy registry [23]. Incident HF was identified using criteria described in the HF guidelines of the European Society of Cardiology [10]. Blood pressure was measured using an automatic Dinamap XL Model 9300 series device and ten blood pressure measurements were taken during 10 min; systolic and diastolic blood pressures were calculated as the mean of the last two measurements. Hypertension was defined as systolic blood pressure  $> 140$  mm Hg, diastolic blood pressure  $> 90$  mm Hg or self-reported usage of antihypertensive medication. Body-mass index ( $\text{kg}/\text{m}^2$ ) was calculated as the ratio of weight to (height)<sup>2</sup>. Waist-hip ratio was calculated as the ratio between minimal waist circumference and hip circumference. Hypercholesterolaemia was defined as total serum cholesterol  $\geq 6.5$  mmol/L (251 mg/dL) or a serum cholesterol  $\geq 5.0$  mmol/L (193 mg/dL) if a history of myocardial infarction (MI) was present or when lipid lowering medication was used. History of MI or cerebrovascular accident (CVA) was defined as participant-reported hospitalization for  $\geq 3$  days as a result of this condition. Smoking status of the patient was determined based on self-reports. Smoking was defined as current smoking or smoking cessation within the previous year. Glomerular filtration rate was estimated using the simplified modification of diet in renal disease (sMDRD) formula [24]. UAE was given as the mean of the two consecutive 24-hour urine collections.

### 2.3. Statistical analysis

All statistical analyses were carried out using STATA, version 14 and a  $p$ -value  $< 0.05$  indicates statistical significance. As the PREVEND cohort has an overrepresentation of subjects with increased UAE, a statistical correction factor was employed using a weighted Cox regression model, so that the conclusions may be extended to the general population [10,11]. A weighing factor of 11.92 was assigned to people with UAE  $< 10$  mg/L and a weighing factor of 1.66 to those with UAE  $> 10$  mg/mL, based on unequal inclusion probabilities. Normally distributed data are presented as mean  $\pm$  standard deviation (SD) and data that are not normally distributed are presented as median  $\pm$  interquartile range (IQR). Categorical variables are presented as percentages. Skewed variables were 2-log transformed in order to facilitate interpretation, i.e. in these cases, the risk estimates should be interpreted as the relative risk if the values of variables were doubled (e.g. from 1 mg/L to 2 mg/L).

Differences between two groups for normally distributed data were tested using two sample  $t$ -test while a Wilcoxon rank-sum test was used for non-normally distributed data. Differences between categorical variables were tested using Pearson's chi-square test. To estimate incidences of DM and HF, we used the Nelson-Aalen cumulative risk estimator. Proportionality assumptions were assessed with Schoenfeld residuals and Cox-proportional hazards models were fitted to the data; crude hazard ratios (HR) were evaluated to assess the univariate association of individual HF biomarkers with new-onset DM. Those variables that displayed a statistical significance in this univariable model were further analysed using three models. The first model was adjusted for age and sex and only those variables that reached significance ( $p < 0.1$ ) were included in the second multivariable model, which was also adjusted for classical risk factors of DM [25]. Those biomarkers that reached a significance of  $p < 0.05$  in the second model were included in the third model which also corrected for insulin resistance. Models that did not fulfil proportionality assumptions were also assessed with logistic regression to give odds ratio (OR). Results are summarized as HRs or ORs with 95% confidence intervals (CIs) based on standard error estimates. Interpretation of the final results was done after performing a Bonferroni type adjustment for multiple analyses, and a  $p$  value  $< 0.0125$  ( $=0.05/4$ ) was deemed significant.

## 3. Results

### 3.1. Clinical characteristics at baseline

The study included 7953 participants that were free from both HF and DM at baseline. Subject characteristics were divided according

to the incidence of DM [see Table 1]. Individuals who developed DM were typically older and predominantly male ( $N = 59\%$ ), with a more frequent history of MI and CVA compared to those that did not develop DM. Comorbidities such as hypertension, hypercholesterolaemia, and obesity were more common in those who developed T2DM. Furthermore, they had higher triglyceride levels and insulin resistance (HOMA-IR) index, and exhibited impairment of renal function with elevated serum creatinine, increased mean 24-hour UAE and reduced eGFR. Several HF biomarkers were also significantly higher in the diabetic subgroup but stretch-related markers NT-proBNP and MR-proANP, and markers of the renin-angiotensin-aldosterone axis showed no significant differences between the groups.

### 3.2. Reciprocal relation between HF and DM

#### 3.2.1. DM incidence

The incidence of new-onset DM was 5.6% during the follow up period of 11 years ( $N = 447/7953$ ) as shown in [Fig. 1a]. There was a 119% increase in the risk of developing DM in participants who developed HF; total incidence of DM in participants who developed HF was 11.8% ( $N = 38/322$ ), versus 5.4% (409/7631) in those who did not develop HF ( $p < 0.001$ ) [Fig. 1b].

#### 3.2.2. HF incidence

The 11-year incidence of new-onset HF was 4.0% ( $N = 321/7953$ ) [Fig. 1c] and there was a 113% increase in the risk of developing HF in participants who developed DM. The incidence of HF in participants who developed DM was 8.5% ( $N = 38/447$ ), versus 3.8% ( $N = 283/7506$ ) in those who did not develop DM ( $p < 0.001$ ) [Fig. 1d].

### 3.3. Temporal association of HF and DM

Around 0.48% of the participants ( $N = 38/7953$ ) developed both DM and HF, and in this subgroup 32% developed DM after HF. The mean duration of onset of HF was  $4.1 \pm 2.0$  years and that of DM was  $6.5 \pm 2.2$  years; the average duration of onset of DM after HF was  $2.4 \pm 1.8$  years. The remaining 68% developed DM before HF; the mean duration of onset of DM was  $5.3 \pm 2.0$  years, the mean duration of onset of HF was  $9.1 \pm 2.3$  years and the average duration of HF onset after DM was  $3.8 \pm 2.5$  years.

### 3.4. Association of insulin resistance and central obesity with HF

Further analysis revealed that participants who developed HF but did not develop DM ( $N = 283$ ) demonstrated a significant increase in insulin resistance [HOMA-IR: 1.92 (1.37–3.09) vs 1.57 (1.07–2.43),  $p < 0.001$ ] and also had elevated serum glucose levels at baseline ( $5.0 \pm 0.7$  mmol/L vs  $4.7 \pm 0.6$  mmol/L,  $p < 0.001$ ) compared to those who did not develop both HF and DM ( $N = 7223$ ) [Supplement 2]. Additionally, we observed that participants who developed both DM and HF had a significantly higher waist-hip ratio (central obesity) compared to those who only developed DM [Supplement 1].

### 3.5. Relationship of HF biomarkers with new-onset DM

Firstly, we validated the association of “HF biomarkers” with new-onset HF [26] [Supplement 4]. Then, the relationship between HF and new-onset DM was evaluated using 15 biomarkers that addressed various pathophysiological scenarios occurring in HF [Table 2]. The classic HF markers, NT-proBNP and MR-proANP and markers of neuroendocrine activation, renin and aldosterone displayed no predictive value in new-onset DM.

Those biomarkers that were significantly associated with new-onset DM in the crude analyses were further analysed using three models to characterize a potentially independent association of HF biomarkers with new-onset DM. PAI-1, hs-CRP, procalcitonin, co-peptin, MR-

**Table 1**Baseline characteristics of subjects ( $N = 7953$ ) according to the status of diabetes mellitus.

		Subjects that did not develop diabetes mellitus $N = 7506$	Subjects that developed diabetes mellitus $N = 447$	$p$ value
Age & Sex	Age (years)	48.6 $\pm$ 12.6	54.8 $\pm$ 10.4	<0.001
	Sex (female), $N$ (%)	3880 (51.7%)	182 (40.7%)	<0.001
Medical history	Smoking (last 1 year), $N$ (%)	2869 (38.3%)	164 (36.7%)	0.490
	Hypertension, $N$ (%)	1857 (24.7%)	219 (49.0%)	<0.001
	Hypercholesterolaemia, $N$ (%)	1885 (25.4%)	176 (39.9%)	<0.001
	Myocardial infarction, $N$ (%)	404 (5.5%)	38 (8.7%)	0.005
	CVA, $N$ (%)	67 (0.9%)	11 (2.5%)	0.001
Anthropometry	BMI, kg/m <sup>2</sup>	25.8 $\pm$ 4.1	29.4 $\pm$ 4.6	<0.001
	Waist-hip ratio	0.87 $\pm$ 0.09	0.94 $\pm$ 0.08	<0.001
Haemodynamic parameters	Systolic BP, mm Hg	127.8 $\pm$ 19.8	140.1 $\pm$ 20.3	<0.001
	Diastolic BP, mm Hg	73.6 $\pm$ 9.6	78.7 $\pm$ 9.5	<0.001
Blood chemistry	Cholesterol, mmol/L	5.6 $\pm$ 1.1	6.0 $\pm$ 1.2	<0.001
	LDL, mmol/L	3.7 $\pm$ 1.1	4.0 $\pm$ 1.0	<0.001
	Triglycerides, mmol/L	1.1 (0.8–1.6)	1.7 (1.2–2.5)	<0.001
	HDL, mmol/L	1.3 $\pm$ 0.4	1.1 $\pm$ 0.3	<0.001
	Glucose, mmol/L	4.7 $\pm$ 0.6	5.6 $\pm$ 0.8	<0.001
	Insulin, mIU/L	7.7 (5.4–11.3)	13.0 (8.8–19.4)	<0.001
	HOMA-IR	1.58 (1.08–2.45)	3.20 (2.13–5.08)	<0.001
	Serum creatinine, $\mu$ mol/L	83.5 $\pm$ 15.1	86.3 $\pm$ 18.0	<0.001
	eGFR, mL/min per 1.73m <sup>2</sup>	80.8 $\pm$ 14.4	78.9 $\pm$ 14.6	<0.007
	UAE, mg/24 h	9.1 (6.2–16.2)	13.4 (7.8–33.8)	<0.001
	Cystatin-C, mg/L	0.77 (0.69–0.87)	0.81 (0.72–0.92)	<0.001
	hs-TnT, ng/L	2.5 (2.5–4.0)	3.0 (2.5–6.0)	<0.001
	NT-proBNP, ng/L	38.0 (17.2–73.5)	33.6 (14.6–70.3)	0.130
Heart failure biomarkers	MR-proANP, pmol/L	47.7 (34.8–64.9)	47.4 (32.5–66.7)	0.720
	Co-peptin, pmol/L	4.6 (2.8–7.4)	5.6 (3.5–8.3)	<0.001
	Renin, mIU/mL	18.0 (11.1–28.3)	18.3 (10.1–29.1)	0.860
	Aldosterone, pg/mL	117.9 (92.9–152.1)	118.1 (91.5–153.4)	0.800
	MR-proADM, nmol/L	0.37 (0.29–0.45)	0.42 (0.33–0.50)	<0.001
	CT-proET-1, pmol/L	34.4 (24.4–43.8)	37.2 (25.7–47.5)	<0.001
	PAI-1, ng/mL	67.6 (39.5–117.7)	124.2 (81.5–189.8)	<0.001
	hs-CRP, mg/L	1.2 (0.5–2.8)	2.1 (1.1–4.5)	<0.001
	Procalcitonin, ng/L	1.6 (1.3–1.9)	1.8 (1.5–2.2)	<0.001
	Galectin-3, ng/mL	10.8 (9.0–13.0)	11.3 (9.8–13.9)	<0.001

CVA, cerebrovascular accident; BMI, body-mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment (estimated insulin resistance); eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; hs-TnT, high-sensitive troponin-T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-A-type natriuretic peptide; MR-proADM, mid-regional pro-adrenomedullin; CT-proET-1, C-terminal pro-endothelin-1; PAI-1, plasminogen activator inhibitor-1; hs-CRP, high-sensitive C-reactive protein.

proADM and UAE remained significantly associated with new-onset DM ( $p$  value < 0.05) in the first model after adjusting for age and sex. These biomarkers, together with those that had a  $p$  value < 0.1 in the first model i.e. hs-TnT and cystatin-C, were analysed using the second model, which was also adjusted for classical risk factors of DM, namely smoking, hypertension, waist-hip ratio and family history of DM. After multivariable adjustment only hs-CRP, procalcitonin, PAI-1 and copeptin had an independent association with new-onset DM ( $p$  < 0.05). After also adjusting for insulin resistance in the third fully-adjusted model, only the inflammation-related biomarkers hs-CRP [hazard ratio (HR) 1.16, (95% CI 1.05 to 1.29),  $p = 0.005$ ], procalcitonin [HR 1.34, (95% CI 1.07 to 1.69),  $p = 0.012$ ] and PAI-1 [HR 1.55, (95% CI 1.37 to 1.75),  $p < 0.001$ ] remained independently associated with new-onset DM. Copeptin displayed a trend towards association [HR 1.18 (1.01–1.38),  $p = 0.033$ ]. Logistic regression was performed in models that demonstrated a significant interaction with time and the results were similar to Cox regression models [Supplement 3].

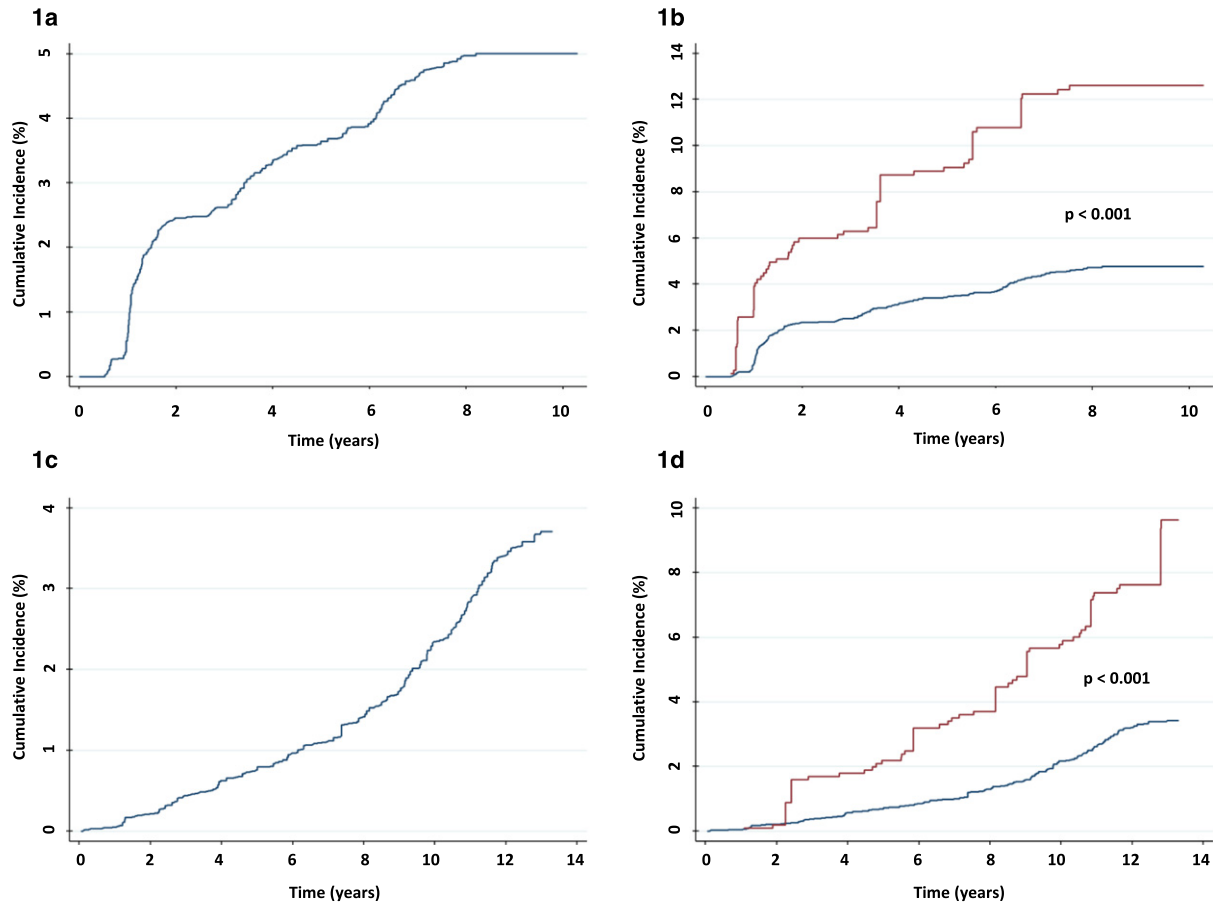
#### 4. Discussion

We demonstrate the reciprocal relationship between HF and DM in a large cohort of the general population, with each disorder increasing the risk of development of the other. This study aimed to identify common pathophysiological pathways underlying HF and DM, and to provide a deeper insight into mechanisms by which HF can cause DM. To this end, we utilized 15 biomarkers reflecting different pathophysiological

scenarios occurring in HF and evaluated their relationship with new-onset DM.

Our results indicate that classic HF biomarkers (i.e. NT-proBNP, MR-proANP and hs-TnT), which significantly predict HF development, did not have any predictive value in the incidence of T2DM. On the other hand, biomarkers related to inflammation, hs-CRP, procalcitonin and PAI-1 were significantly associated with DM, even after multivariable correction and displayed a predictive utility in new-onset DM. Increasing levels of copeptin (surrogate marker of vasopressin) also increased the risk of new-onset DM; although copeptin reflects neurohormonal activation, it could also be associated with systemic inflammatory responses through indirect mechanisms involving hypertension and endothelial dysfunction [27,28].

DM is an established risk factor for HF and is involved in cardiac damage through various macrovascular and microvascular mechanisms, and also via direct cardiotoxic effects of hyperglycaemia and hyperinsulinaemia [29]. HF is also an independent risk factor for the development of T2DM (cardiac diabetes), however, underlying pathophysiological mechanisms are poorly characterized [4,5]. In our study, we observed that participants who developed HF, but remained free of DM ( $N = 283$ ) were also insulin-resistant, and had significantly elevated baseline serum glucose levels compared to those that did not develop HF and DM, indicating that insulin resistance and hyperglycaemia are closely associated with HF even before the clinical diagnosis of HF is established, and such individuals should therefore be more intensively screened for HF.



**Fig. 1.** (1a) Incidence of new-onset DM in 11 ( $\pm 3$ ) years starting from the second visit. (1b) Incidence of new-onset DM stratified by HF starting from the second visit (1c) Cumulative incidence of new-onset HF in 11 ( $\pm 3$ ) years starting from the first visit (1d) Cumulative incidence of new-onset HF stratified by DM starting from the first visit. HF, heart failure; DM, diabetes mellitus.

**Table 2**

Relationship of HF biomarkers with new-onset DM in 7953 subjects free of DM and HF\*.

	Biomarkers	Univariable	<i>p</i> value	Model 1	<i>p</i> value	Model 2	<i>p</i> value	Model 3	<i>p</i> value
		HR (95% CI)		Adjusted for age, sex HR (95% CI)		Multivariable adjusted ‡ HR (95% CI)		Fully adjusted § HR (95% CI)	
Myocardial injury & stretch	hs-TnT	1.58 (1.42–1.77)	<0.001	1.19 (0.99–1.43)	0.064	1.12 (0.92–1.36)	0.261	–	
	NT-proBNP	0.96 (0.87–1.07)	0.453	–		–		–	
	MR-proANP	1.07 (0.85–1.35)	0.545	–		–		–	
Endothelial markers	CT-proET-1	1.02 (1.01–1.03)	0.001	1.01 (0.99–1.02)	0.320	–		–	
Neuroendocrine activation	Renin	0.99 (0.85–1.15)	0.877	–		–		–	
	Aldosterone	1.10 (0.86–1.40)	0.460	–		–		–	
	Co-peptin	1.37 (1.20–1.57)	<0.001	1.23 (1.06–1.44)	0.008	1.19 (1.02–1.39)	0.025	1.18 (1.01–1.38)	0.033
Inflammation	MR-proADM	2.22 (1.56–3.16)	<0.001	1.49 (1.03–2.15)	0.032	1.28 (0.91–1.81)	0.160	–	
	hs-CRP	1.33 (1.24–1.44)	<0.001	1.31 (1.20–1.42)	<0.001	1.22 (1.11–1.35)	<0.001	1.16 (1.05–1.29)	0.005
	Procalcitonin	1.78 (1.56–2.03)	<0.001	1.54 (1.31–1.80)	<0.001	1.48 (1.25–1.76)	<0.001	1.34 (1.07–1.69)	0.012
Fibrosis	PAI-1	1.89 (1.71–2.09)	<0.001	1.79 (1.61–2.00)	<0.001	1.64 (1.46–1.84)	<0.001	1.55 (1.37–1.75)	<0.001
	Galectin-3	1.52 (1.17–1.97)	0.002	1.18 (0.88–1.58)	0.280	–		–	
Kidney function	UAE	1.30 (1.21–1.39)	<0.001	1.19 (1.10–1.30)	<0.001	1.08 (0.98–1.18)	0.115	–	
	Cystatin-C	2.30 (1.62–3.27)	<0.001	1.43 (0.99–2.07)	0.055	1.34 (0.98–1.85)	0.070	–	
	Creatinine	1.02 (1.01–1.02)	<0.001	1.00 (0.99–1.01)	0.526	–		–	

HF – heart failure; DM – diabetes mellitus.

CI, confidence interval; HR, hazard ratio; hs-TnT, high-sensitive troponin-T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-A-type natriuretic peptide; CT-proET-1, C-terminal pro-endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; hs-CRP, high-sensitive C-reactive protein; PAI-1, plasminogen activator inhibitor-1; UAE, urinary albumin excretion.

\* Hazard ratios for CT-proET-1 and creatinine are presented per unit increase. Hazard ratios for other biomarkers are presented per doubling of biomarker.

Biomarkers with *p*-value < 0.1 in Model 1 were included for further analysis using Model 2

‡ Adjusted for age, sex, smoking status, hypertension, waist-hip ratio and family history of diabetes mellitus.

Proportional hazards were not satisfied in these models, and therefore can be interpreted as an “average effect” over time points that are observed in our dataset.

Biomarkers with a *p*-value < 0.05 in Model 2 were included for analysis in the fully adjusted Model 3.

§ Adjusted for all variables in multivariable model and also for insulin resistance.



Myocardial insulin resistance, especially in the scenario of HF could be dangerous. HF leads to systemic hypoxia and to maximize energy efficiency under such conditions, the failing heart shifts its metabolism from fatty acids to glucose as the major fuel [30]; when superimposed with the myocardial insulin resistant state, utilization of glucose as an alternate energy substrate is also hampered resulting in exacerbation of the pre-existing HF. Therefore, HF patients should also be more intensively monitored for (myocardial) insulin resistance.

To the best of our knowledge, there are no prospective cohort studies that describe the temporal associations of DM and HF. This study reveals that DM can either precede or follow HF, and validates that HF is an insulin resistant state. It has been demonstrated in other studies that VAD improved insulin resistance in HF patients significantly [8], and therefore we speculated that markers of myocardial stretch (i.e. natriuretic peptides) would be associated with T2DM as haemodynamic unloading improved glycaemic parameters. This was not the case and our results indicate that classic HF biomarkers might not be related to the pathophysiological mechanisms of new-onset DM. However, inflammation-related biomarkers significantly predict new-onset DM, this strongly suggests that an indirect “inflammatory” pathway links HF biomarkers to new-onset DM [Fig. 2]. It also leads us to hypothesise that HF could cause T2DM through complex immuno-inflammatory mechanisms.

Systemic inflammation is an important risk factor for HF [31,32]; some risk-prediction charts already incorporate hs-CRP in HF risk estimation [33] and JUPITER study demonstrated that the excess cardiovascular risk associated with inflammation (hsCRP) is amenable to statin therapy [34]. Elevated procalcitonin levels are associated with a worse prognosis in HF patients, even in those with no evidence of infection, suggesting that co-existing systemic inflammation could be responsible for clinical deterioration of these patients [35]. Although PAI-1 is a surrogate marker of endothelial thrombo-inflammation [36,37], its role in HF seems to be ambiguous; elevated PAI-1 levels increase the risk of MI in individuals [38], however, genetic inhibition of PAI-1 in murine models displays severe cardiac-specific fibrosis [39].

Inflammatory pathways are also indicated in the pathogenesis of DM, and adipose tissue appears to be a source of various inflammatory proteins. Our study shows that elevated PAI-1 levels were strongly associated with the incidence of new-onset DM. Individuals who developed T2DM also demonstrated a significant increase in waist-hip ratio, indicating that PAI-1, DM and central obesity are closely related. This is also in line with previous studies that demonstrated a significant

association between PAI-1 levels and the amount of visceral adipose tissue [40]; overexpression of PAI-1 has also been observed in cultured adipocytes and in adipose tissue of mice and humans [41] strengthening the concept that (visceral) adipose tissue is an important source of PAI-1. Interestingly, PAI-1 KO mouse models on high-fat diet displayed a significant reduction in obesity, hyperglycaemia and hyperinsulinaemia compared to wild type mice fed on a similar diet [42]. Thus, it is highly plausible that visceral adipose tissue affects the glycaemic balance of the body through PAI-1, and that PAI-1 could be a therapeutic target in DM and obesity.

Procalcitonin, usually mentioned in the context of infection, could also be elevated in obesity-associated low-grade inflammation. Several studies have demonstrated that procalcitonin is associated with chronic low-grade inflammation, obesity and insulin resistance in the general population [19,25]. In in-vitro experiments, adipocytes stimulated by macrophages secrete procalcitonin, and hypoperfused adipose tissue is widely considered as a non-neuroendocrine depot of procalcitonin [43,44].

CRP is a widely used marker of inflammation, and is secreted by hepatocytes as an acute-phase response to systemic inflammatory triggers. However, recent evidence also indicates alternative sources of CRP in chronic low-grade inflammation, e.g. adipose tissue, suggesting that CRP could have a greater role in obesity-related pathophysiologies, including metabolic syndrome [45].

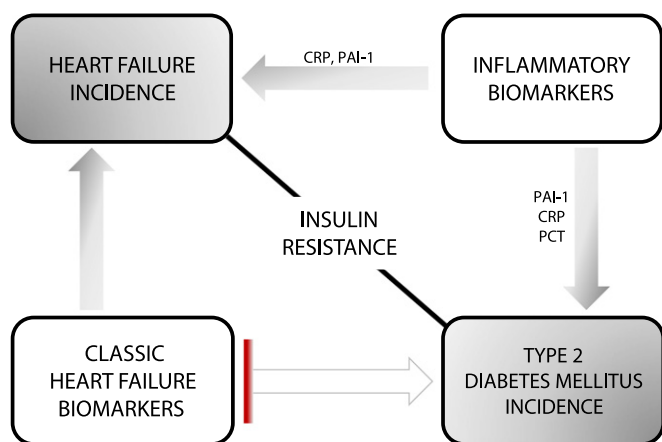
Taken together with the results from our study, common risk factors involving systemic immuno-inflammatory activation appear to play a crucial role in the etiology of both HF and DM, and visceral adipose tissue correlates strongly with the incidence of both these disorders.

Other mechanisms might also operate in HF that increase the risk of new-onset DM. Certain HF medications e.g.  $\beta$ -blockers and thiazide diuretics are known to increase the risk of DM in patients with hypertension [46]. However, data from the NAVIGATOR trial revealed that in patients with impaired glucose tolerance, diuretics were associated with an increased risk of DM while  $\beta$ -blockers and calcium channel blockers were not [47]. We should also acknowledge that, paradoxically, certain anti-inflammatory medications, e.g. statins, used in HF could contribute to the excess risk associated with new-onset DM [47,48]. Nevertheless, this evidence has to be weighed together with the cardiovascular protection offered by these drugs, especially in patients with ischaemia, dyslipidaemia and vascular comorbidities. Finally, NSAIDs are commonly used anti-inflammatory drugs, and appear to lower glucose levels in T2DM [49]. However, they are known to increase cardiovascular risk and also HF-related hospitalizations (depending on the dosage and type of NSAID) [50], raising concerns about their usage in patients with HF.

This study indicates that inflammation plays a key role in HF associated insulin resistance and T2DM, although mechanisms involved in the immuno-inflammatory axis appear to be complex and indirect. Existing anti-inflammatory therapies also give contrasting results in reducing the risk of new-onset DM. Further studies are needed to elucidate the inflammatory mechanisms operating in DM and HF and how anti-inflammatory therapies could affect their incidence rates. Our study also underscores the necessity of developing specific cardioprotective anti-inflammatory therapies that can also reduce the incidence of new-onset DM.

## 5. Clinical perspective

DM and HF frequently coexist and this portends an unfavourable prognosis and increases mortality. Our study reinforces that HF is an independent risk factor for the development of DM. As the prevalence of CHF is increasing, the number of patients developing dysglycaemia and T2DM as a consequence of HF is expected to surge in the coming years. Effective management (anti-inflammatory) strategies to combat concurrent HF and DM need to be urgently developed to address this issue.



**Fig. 2.** Inflammation links insulin resistance in T2DM and HF. Classic HF biomarkers have a predictive value in new-onset HF but are not associated with new-onset DM. On the other hand, inflammation-related biomarkers are significantly associated with the risk of development of both DM and HF, suggesting that complex immuno-inflammatory mechanisms might be responsible for insulin resistance and DM arising against the backdrop of HF. DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; HF, heart failure.

## 6. Study strengths and limitations

Firstly, our study is a large community based cohort with a long follow-up time of  $11 \pm 3$  years. Secondly, temporal associations between HF and DM could be characterized due to its longitudinal design. Finally, biomarkers reflecting a wide spectrum of cardiovascular pathophysiological mechanisms were utilized to evaluate their association with new-onset DM as both these diseases have several shared pathophysiological mechanisms.

We also acknowledge several limitations of our study. PREVENT cohort was enriched for increased UAE and is not an exact representation of the general population; we overcame this over-representation using a statistical correction method. The subjects included were predominantly Caucasian, therefore, extension of the results to other races might not be accurate. Detection bias should also be considered; patients who developed HF are usually screened more intensely and therefore, DM arising after HF could have been detected early. On the other hand, several patients who developed DM might not have reported to the hospital immediately, and the disease could have been undiagnosed for a long time. Long-term storage effects in the samples such as degradation and denaturation must also be taken into account. Furthermore, our study is purely observational and further experimental studies are warranted to identify the source(s) and functions of pro-inflammatory bio-markers, namely PAI-1, procalcitonin and hs-CRP.

## 7. Conclusion

HF is an insulin resistant state and can either follow or precede DM. Although there is a strong reciprocal relationship between HF and DM, classic biomarkers that predict new-onset HF do not have a predictive value in new-onset DM. However, markers of inflammation are closely associated with T2DM. The pathophysiological mechanisms by which HF causes DM is not direct; complex, indirect pathophysiological mechanisms involving inflammation are indicated. Future studies are needed to explore the inflammatory link between HF and DM.

## Conflict of interest

Dr.de Boer is employed by the UMC Groningen that received research funding from AstraZeneca, Bristol-Myers Squibb and Trevena. Dr.de Boer received speaker and advisory board honoraria from Novartis and Roch Diagnostics.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2017.10.035>.

## References

- [1] D. Levy, S. Kenchaiah, M.G. Larson, E.J. Benjamin, M.J. Kupka, K.K.L. Ho, et al., Long-term trends in the incidence of and survival with heart failure, *N. Engl. J. Med.* 347 (2002) 1397–1402.
- [2] C.J. Taylor, A.K. Roalfe, R. Iles, F.D.R. Hobbs, Ten-year prognosis of heart failure in the community: follow-up data from the Echocardiographic Heart of England Screening (ECHOES) study, *Eur. J. Heart Fail.* 14 (2012) 176–184.
- [3] G. Bahtiyar, D. Guterman, H. Lebovitz, Heart failure: a major cardiovascular complication of diabetes mellitus, *Curr. Diab. Rep.* 16 (2016), 116.
- [4] J.W. Swan, S.D. Anker, C. Walton, I.F. Godsland, A.L. Clark, F. Leyva, et al., Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure, *J. Am. Coll. Cardiol.* 30 (1997) 527–532.
- [5] W. Doehner, S. von Haehling, S.D. Anker, Insulin resistance in chronic heart failure, *J. Am. Coll. Cardiol.* 52 (2008) 239 author reply 239–40.
- [6] S.L. Kristensen, D. Preiss, P.S. Jhund, I. Squire, J.S. Cardoso, B. Merkely, et al., Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial, *Circ. Heart Fail.* 9 (2016) 1–12.
- [7] P. Gargiulo, P. Perrone-Filardi, Heart failure, whole-body insulin resistance and myocardial insulin resistance: an intriguing puzzle, *J. Nucl. Cardiol.* (2016) 1–4.
- [8] A. Chokshi, K. Drosatos, F.H. Cheema, R. Ji, T. Khawaja, S. Yu, et al., Ventricular assist device implantation corrects myocardial lipotoxicity, reverses insulin resistance, and normalizes cardiac metabolism in patients with advanced heart failure, *Circulation* 125 (2012) 2844–2853.
- [9] R.A. de Boer, N.F. Schrotten, S.J.L. Bakker, H. Mahmud, M.K. Szymanski, P. van der Harst, et al., Plasma renin and outcome in the community: data from PREVENT, *Eur. Heart J.* 33 (2012) 2351–2359.
- [10] F.P. Brouwers, R.A. de Boer, P. van der Harst, A.A. Voors, R.T. Gansevoort, S.J. Bakker, et al., Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVENT, *Eur. Heart J.* 34 (2013) 1424–1431.
- [11] E.G. Marcos, B. Geelhoed, P. Van Der Harst, S.J.L. Bakker, R.T. Gansevoort, H.L. Hillege, et al., Relation of renal dysfunction with incident atrial fibrillation and cardiovascular morbidity and mortality: the PREVENT study, *Europace* (2017) <https://doi.org/10.1093/europace/euw373>.
- [12] L. Scheven, P.E. de Jong, H.L. Hillege, H.J. Lambers Heerspink, L.J. van Pelt, J.E. Kootstra, et al., High-sensitive troponin T and N-terminal pro-B type natriuretic peptide are associated with cardiovascular events despite the cross-sectional association with albuminuria and glomerular filtration rate, *Eur. Heart J.* 33 (2012) 2272–2281.
- [13] G.C.M. Linssen, S.J.L. Bakker, A.A. Voors, R.T. Gansevoort, H.L. Hillege, P.E. de Jong, et al., N-Terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population, *Eur. Heart J.* 31 (2010) 120–127.
- [14] K.J.J. van Hateren, A. Alkhalaf, N. Kleefstra, K.H. Groenier, P.E. de Jong, D. de Zeeuw, et al., Comparison of midregional pro-A-type natriuretic peptide and the N-terminal pro-B-type natriuretic peptide for predicting mortality and cardiovascular events, *Clin. Chem.* 58 (2012) 293–297.
- [15] N. Verweij, H. Mahmud, I. Mateo Leach, R.A. de Boer, F.P. Brouwers, H. Yu, et al., Genome-wide Association Study on Plasma Levels of Midregional-proadrenomedullin and C-terminal-pro-endothelin-1, *Hypertens. (Dallas, Tex 1979)*, 61, 2013 602–608.
- [16] E. Meijer, S.J.L. Bakker, N. Halbesma, P.E. de Jong, J. Struck, R.T. Gansevoort, Copeptin, a surrogate marker of vasopressin, is associated with microalbuminuria in a large population cohort, *Kidney Int.* 77 (2010) 29–36.
- [17] F.P. Brouwers, R.A. de Boer, P. van der Harst, J. Struck, P.E. de Jong, D. de Zeeuw, et al., Influence of age on the prognostic value of mid-regional pro-adrenomedullin in the general population, *Heart* 98 (2012) 1348–1353.
- [18] E.M. Stuvelling, H.L. Hillege, S.J.L. Bakker, F.W. Asselbergs, P.E. de Jong, R.O.B. Gans, et al., C-reactive protein and microalbuminuria differ in their associations with various domains of vascular disease, *Atherosclerosis* 172 (2004) 107–114.
- [19] A. Abbasi, E. Corpeleijn, D. Postmus, R.T. Gansevoort, P.E. de Jong, R.O.B. Gans, et al., Plasma procalcitonin is associated with obesity, insulin resistance, and the metabolic syndrome, *J. Clin. Endocrinol. Metab.* 95 (2010) E26–31.
- [20] C.S. Coffey, F.W. Asselbergs, P.R. Hebert, H.L. Hillege, Q. Li, J.H. Moore, et al., The association of the metabolic syndrome with PAI-1 and t-PA levels, *Cardiol. Res. Pract.* 2011 (2011), 541467.
- [21] R.A. de Boer, D.J. van Veldhuisen, R.T. Gansevoort, A.C. Muller Kobold, W.H. van Gilst, H.L. Hillege, et al., The fibrosis marker galectin-3 and outcome in the general population, *J. Intern. Med.* 272 (2012) 55–64.
- [22] H.L. Hillege, V. Fidler, G.F.H. Diercks, W.H. van Gilst, D. de Zeeuw, D.J. van Veldhuisen, et al., Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population, *Circulation* 106 (2002) 1777–1782.
- [23] S.E. Inzucchi, R.M. Bergenstal, J.B. Buse, M. Diamant, E. Ferrannini, M. Nauck, et al., Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), *Diabetes Care* 35 (2012) 1364–1379.
- [24] T.D.J. Smilde, D.J. van Veldhuisen, G. Navis, A.A. Voors, H.L. Hillege, Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction, *Circulation* 114 (2006) 1572–1580.
- [25] A. Abbasi, E. Corpeleijn, D. Postmus, R.T. Gansevoort, P.E. de Jong, R.O.B. Gans, et al., Plasma procalcitonin and risk of type 2 diabetes in the general population, *Diabetologia* 54 (2011) 2463–2465.
- [26] F.P. Brouwers, W.H. van Gilst, K. Damman, M.P. van den Berg, R.T. Gansevoort, S.J.L. Bakker, et al., Clinical risk stratification optimizes value of biomarkers to predict new-onset heart failure in a community-based cohort, *Circ. Heart Fail.* 7 (2014) 723–731.
- [27] C. Savoia, E.L. Schiffrin, Vascular inflammation in hypertension and diabetes: molecular mechanisms and therapeutic interventions, *Clin. Sci. (Lond.)* 112 (2007) 375–384.
- [28] I. Kocyigit, M.I. Yilmaz, O. Gungor, E. Eroglu, A. Unal, O. Orselik, et al., Vasopressin-related copeptin is a novel predictor of early endothelial dysfunction in patients with adult polycystic kidney disease, *BMC Nephrol.* 17 (2016), 196.

- [29] P.M. Seferović, I. Milinković, A.D. Ristić, J.P. Seferović Mitrović, K. Lalić, A. Jotić, et al., Diabetic cardiomyopathy: ongoing controversies in 2012, *Herz* 37 (2012) 880–886.
- [30] T. Doenst, T.D. Nguyen, E.D. Abel, Cardiac metabolism in heart failure: implications beyond ATP production, *Circ. Res.* 113 (2013) 709–724.
- [31] N. Suthahar, W.C. Meijers, H.H.W. Silljé, R.A. de Boer, From inflammation to fibrosis—molecular and cellular mechanisms of myocardial tissue remodelling and perspectives on differential treatment opportunities, *Curr. Heart Fail. Rep.* (2017) <https://doi.org/10.1007/s11897-017-0343-y>.
- [32] I. Kardys, A.M. Knetsch, G.S. Bleumink, J.W. Deckers, A. Hofman, B.H.C. Stricker, et al., C-reactive protein and risk of heart failure. The Rotterdam study, *Am. Heart J.* 152 (2006) 514–520.
- [33] P.M. Ridker, N.P. Paynter, N. Rifai, J.M. Gaziano, N.R. Cook, C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men, *Circulation* 118 (2008) 2243–2251 (4 pp. following 2251).
- [34] A. Verma, C.J. Lavie, R.V. Milani, C-reactive protein: how has JUPITER impacted clinical practice? *Ochsner J* 9 (2009) 204–210.
- [35] M.P. Villanueva, A. Mollar, P. Palau, A. Carratalá, E. Núñez, E. Santas, et al., Procalcitonin and long-term prognosis after an admission for acute heart failure, *Eur. J. Intern. Med.* 26 (2015) 42–48.
- [36] E.K.O. Kruihof, Regulation of plasminogen activator inhibitor type 1 gene expression by inflammatory mediators and statins, *Thromb. Haemost.* 100 (2008) 969–975.
- [37] I. Juhan-Vague, M.-C. Alessi, A. Mavri, P.E. Morange, Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk, *J. Thromb. Haemost.* 1 (2003) 1575–1579.
- [38] B. Monica Mariana, V. Marius Marcian, PAI-1 inhibition - another therapeutic option for cardiovascular protection, *Maedica* 10 (2015) 147–152.
- [39] K.K. Gupta, D.L. Donahue, M.J. Sandoval-Cooper, F.J. Castellino, V.A. Ploplis, Plasminogen activator inhibitor-1 protects mice against cardiac fibrosis by inhibiting urokinase-type plasminogen activator-mediated plasminogen activation, *Sci Rep* 7 (2017), 365.
- [40] J.H.N. Lindeman, H. Pijl, K. Toet, P.H.C. Eilers, B. van Ramshorst, M.M. Buijs, et al., Human visceral adipose tissue and the plasminogen activator inhibitor type 1, *Int. J. Obes.* 31 (2007) 1671–1679.
- [41] K. Schäfer, K. Fujisawa, S. Konstantinides, D.J. Loskutoff, Disruption of the plasminogen activator inhibitor 1 gene reduces the adiposity and improves the metabolic profile of genetically obese and diabetic ob/ob mice, *FASEB J.* 15 (2001) 1840–1842.
- [42] L. Ma, S. Mao, K.L. Taylor, T. Kanjanabuch, Y. Guan, Y. Zhang, et al., Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1, *Diabetes* 53 (2004) 336–346.
- [43] P. Linscheid, D. Seboek, E.S. Nylen, I. Langer, M. Schlatter, K.L. Becker, et al., In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue, *Endocrinology* 144 (2003) 5578–5584.
- [44] P. Linscheid, D. Seboek, D.J. Schaer, H. Zulewski, U. Keller, B. Müller, Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes, *Crit. Care Med.* 32 (2004) 1715–1721.
- [45] M. Visser, L.M. Bouter, G.M. McQuillan, M.H. Wener, T.B. Harris, Elevated C-reactive protein levels in overweight and obese adults, *JAMA* 282 (1999) 2131–2135.
- [46] D.F. Blackburn, T.W. Wilson, Antihypertensive medications and blood sugar: theories and implications, *Can. J. Cardiol.* 22 (2006) 229–233.
- [47] L. Shen, B.R. Shah, E.M. Reyes, L. Thomas, D. Wojdyla, P. Diem, et al., Role of diuretics,  $\beta$  blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: reanalysis of data from the NAVIGATOR study, *BMJ* 347 (2013), f6745.
- [48] M. Casula, F. Mozzanica, L. Scotti, E. Tragni, A. Pirillo, G. Corrao, et al., Statin use and risk of new-onset diabetes: a meta-analysis of observational studies, *Nutr. Metab. Cardiovasc. Dis.* 27 (2017) 396–406.
- [49] N.L. Mork, R.P. Robertson, Effects of nonsteroidal antiinflammatory drugs in conventional dosage on glucose homeostasis in patients with diabetes, *West. J. Med.* 139 (1983) 46–49.
- [50] N. Pawlosky, Cardiovascular risk: are all NSAIDs alike? *Can. Pharm. J.* 146 (2013) 80–83.